EXHIBIT D

DWORKIN ARTICLE

The Journal of Pain, Vol 8, No 2 (February), 2007: pp 118-126
Available online at www.sciencedirect.com

ELSEVIER

Symptom Profiles Differ in Patients With Neuropathic Versus Non-neuropathic Pain

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Abstract: The distinction between neuropathic and non-neuropathic pain reflects partially distinct mechanisms and patterns of treatment response. It was therefore hypothesized that patients with neuropathic and non-neuropathic pain have different profiles of symptoms and signs. To test this hypothesis, pain intensity, unpleasantness, quality, and spatial characteristics were examined in 618 patients with 1 of 3 peripheral neuropathic pain conditions (painful diabetic peripheral neuropathy, painful idiopathic sensory polyneuropathy, or postherpetic neuralgia), osteoarthritis pain, or low back pain. These assessments were conducted before treatment had begun in clinical trials of lidocaine patch 5% administered alone or with stable dosages of other analgesics. Patients with osteoarthritis pain and low back pain did not differ in their profile of pain quality and spatial characteristics and were combined to form a group of patients with non-neuropathic pain. In univariate analyses, patients with peripheral neuropathic pain reported significantly more intense hot, cold, sensitive, itchy, and surface pain and significantly less intense dull and deep pain than patients with non-neuropathic pain. In a multivariate analysis, the overall pattern of pain quality and spatial characteristics differed significantly between patients with neuropathic and non-neuropathic pain. In addition, specific pain quality and spatial characteristics improved the discrimination of patients with neuropathic and non-neuropathic pain in a logistic regression model that adjusted for demographic covariates and overall pain intensity and unpleasantness.

Perspective: *The results indicate that the distinction between neuropathic and non-neuropathic pain is reflected in different profiles of pain quality and spatial characteristics and suggest that the assessment of patterns of pain symptoms might contribute to the identification of distinct pathophysiologic mechanisms and the development of mechanism-based treatment approaches.*

Key words: *Neuropathic pain, symptoms, pain quality, non-neuropathic pain, low back pain, osteoarthritis pain.*

Received May 3, 2006; Revised June 16, 2006; Accepted June 18, 2006.

Supported by a grant from Endo Pharmaceuticals to the University of Rochester Office of Professional Education. RHD has received research support, consulting fees, or honoraria in the past year from Allergan, Astellas Pharma, Biomedical Development Corporation, Cephalon, Dov Pharmaceuticals, Eli Lilly & Co, Endo Pharmaceuticals, EpiCept Corporation, Fralex Therapeutics, NeurogesX (also stock options), Novartis Pharmaceuticals, Organon, Pfizer, UCB Pharma, US Food and Drug Administration, US National Institutes of Health, Wyeth, and Yamanouchi Europe. MPJ has received research support or consulting fees in the past year from Depomed, Endo Pharmaceuticals, Fralex Therapeutics (also stock options), and Pfizer. ARG is an employee of and holds stock options in Endo Pharmaceuticals.

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1526-5900/$32.00

doi:10.1016/j.jpain.2006.06.005

Beginning with the publication of an influential editorial in 1998,[47] there has been a great deal of attention devoted to implementing a mechanism-based approach for diagnosing, classifying, and treating painful conditions. Rather than diagnosing pain on the basis of clinical disease—for example, diabetic peripheral neuropathy or osteoarthritis—the major goal of such an approach would be to identify the specific pathophysiologic mechanisms of an individual patient's pain and to then target treatment to these specific pain mechanisms.[28,46,49] One important implication of the mechanism-based approach is that patterns of symptoms and signs, which differ greatly among patients, might contribute to the identification of pain mechanisms.[7,17,20,40]

Although support for the potential of a mechanism-based approach is provided by a considerable body of research, with few exceptions it is not possible at present to identify mechanisms of clinical pain in either the research or the clinical setting.[34,36] Nevertheless, there is widespread agreement that the distinction between neuropathic and non-neuropathic pain reflects at least partially distinct mechanisms, which are reflected in somewhat different patterns of treatment efficacy. It can therefore be hypothesized that patients with neuropathic and non-neuropathic pain have different profiles of symptoms and signs.

Surprisingly few studies, however, have had a primary objective of characterizing differences in symptoms and signs between patients with neuropathic and non-neuropathic pain. Despite its neglect of some common symptoms of neuropathic pain, the McGill Pain Questionnaire[33] has been used to discriminate various types of neuropathic pain from non-neuropathic pain.[14,32,45] More recently, several measures have been developed to assist in diagnosing neuropathic pain, and various pain symptoms—including burning, cold, electric shock–like, shooting, and stimulus-evoked pain—have been found to be more common in patients with neuropathic pain than in those with non-neuropathic pain.[4,10,11,12,30] Only 2 measures, however, have been developed specifically for evaluating the symptoms of patients with neuropathic pain.[13,20] Although the symptoms included in these measures overlap with those included in the measures designed for diagnosing neuropathic pain, these 2 measures were designed to characterize the most important symptoms of neuropathic pain rather than to assess the subset of symptoms that are most diagnostically discriminating.

The primary objective of the present study was to determine whether there are differences in pain quality between patients with peripheral neuropathic pain and those with non-neuropathic inflammatory and musculoskeletal pain. We used the Neuropathic Pain Scale (NPS),[20] which includes ratings of 6 specific pain qualities (sharp, hot, dull, cold, sensitive, and itchy) and 2 ratings of spatial characteristics (specifically, deep and surface pain). The NPS also includes ratings of overall pain intensity and pain unpleasantness, which are not only critically important in the overall experience of pain,[37] but are also significantly associated with ratings of specific neuropathic pain symptoms.[5] To adequately characterize group differences in pain quality and spatial characteristics, it is therefore necessary to control for overall pain intensity and unpleasantness, and the NPS makes this possible with administration of a single measure.

Materials and Methods

Study Participants and Procedures

All data examined in the present report were collected at baseline visits before treatment had begun in clinical trials of lidocaine patch 5%.[6,15,18,21,23,24,44] Analyses of changes with lidocaine patch 5% treatment in several of these studies for NPS items and scales and of the relationships between NPS items and physical and emotional functioning have been reported previously.[2,19,22,26,27] All participants provided informed consent before any study procedures were initiated. The protocols conformed to the 1975 Declaration of Helsinki and were approved by the following institutional review boards: Biomedical Research Alliance of New York Institutional Review Board (Great Neck, NY), Hackensack University Medical Center Institutional Review Board (Hackensack, NJ), IntegReview Ethical Review Board (Austin, TX), Lehigh Valley Hospital Institutional Review Board (Allentown, PA), VA Hospital Human Subjects Committee (Madison, WI), and Western Institutional Review Board (Seattle, WA).

To participate in the trials, patients had to have an average daily pain intensity that was either >4 or ≥4 (depending on the trial) on a 0-10 numerical rating scale and remain on a stable analgesic regimen for at least 1 week before study entry. Exclusion criteria for all trials included: a positive pregnancy test, the presence of another chronic pain condition that might interfere with assessment of pain relief, open skin lesions in the area(s) where patches were to be applied, known hypersensitivity to lidocaine or amide anesthetics, current treatment with class I antiarrhythmic agents, history of excessive alcohol use or illicit drug use, and history of suicide attempt or current suicide intent or plan. Several of the trials had additional exclusion criteria, for example, seeking or receiving Worker's Compensation or Social Security benefits or evidence of secondary gain for pain[44] and history of more than 1 back surgery or back surgery within 3 months of study entry.[23]

Participants were 618 patients with peripheral neuropathic pain, low back pain, or osteoarthritis pain. Baseline NPS data were available for 135 patients with either painful diabetic peripheral neuropathy,[6,44] painful idiopathic sensory polyneuropathy,[24] or postherpetic neuralgia[44] (in prior analyses, 133 of these patients who had treatment outcome data available were combined to form a group of patients with peripheral neuropathic pain[26]). This group of patients was compared with a subset of 37 patients with the same 3 conditions from a trial of peripheral neuropathic pain[18] for age using a *t* test, for sex and race using chi-square tests, and for the interaction of group with the 8 baseline NPS pain quality and spatial items controlling for age, sex, race, and overall

Table 1. Group Differences in Neuropathic Pain Scale (NPS) Item Scores

NPS Item	Low Back Pain (LBP), Mean (SD)	Osteoarthritic Pain (OA), Mean (SD)	Neuropathic Pain (NP), Mean (SD)	LBP vs OA, Difference (SD)	LBP vs NP, Difference (SD)	OA vs NP, Difference (SD)
Sharp	5.77 (2.99)	6.21 (2.76)	6.33 (2.74)	.44 (2.90)	−.56* (2.89)	.12 (2.75)
Hot	3.66 (3.01)	3.84 (2.79)	5.41 (3.06)	−.18 (2.93)	−1.75*** (3.03)	1.57*** (2.93)
Dull	5.19 (2.79)	5.01 (2.62)	4.61 (2.82)	.18 (2.73)	.58* (2.80)	−.40 (2.72)
Cold	1.10 (2.11)	1.44 (2.26)	3.94 (3.58)	−.34 (2.17)	−2.83*** (2.76)	2.50*** (3.00)
Sensitive	2.24 (2.78)	2.52 (2.87)	4.97 (3.48)	−.28 (2.82)	−2.73*** (3.07)	2.45***(3.20)
Itchy	1.26 (2.24)	1.35 (2.09)	2.51 (3.09)	−.09 (2.18)	−1.25*** (2.60)	1.16*** (2.65)
Deep	7.58 (1.72)	7.46 (1.99)	6.94 (2.38)	.12 (1.83)	.64** (2.00)	−.52* (2.20)
Surface	4.21 (2.77)	4.39 (2.74)	6.11 (2.57)	−.18 (2.76)	−1.90*** (2.70)	1.72*** (2.66)
Intense	6.96 (1.66)	6.83 (2.00)	7.13 (1.75)	.12 (1.80)	−.18 (1.70)	.30 (1.88)
Unpleasant	7.42 (1.78)	6.65 (1.95)	7.45 (1.89)	.77*** (1.85)	−.03 (1.82)	.81*** (1.92)

*$P < .05$, for 2-tailed t tests of differences in means for patients with low back pain, osteoarthritis pain, and neuropathic pain.

**$P < .01$, for 2-tailed t tests of differences in means for patients with low back pain, osteoarthritis pain, and neuropathic pain.

***$P < .001$, for 2-tailed t tests of differences in means for patients with low back pain, osteoarthritis pain, and neuropathic pain.

pain intensity and unpleasantness using multivariate analysis of covariance (MANCOVA). There were no significant differences, and these 2 groups were therefore combined to form a sample of 172 patients with peripheral neuropathic pain.

Baseline NPS data were available for 178 patients with acute/subacute, short-term chronic, or long-term chronic low back pain[23,44] (in prior analyses, 175 of these patients who had treatment outcome data available were combined to form a group of patients with low back pain[26]). This group of patients was compared with 101 patients with low back pain enrolled in an unpublished trial for age using a t test, for sex and race using chi-square tests, and for the interaction of group with the 8 baseline NPS pain quality and spatial items controlling for age, sex, race, and overall pain intensity and unpleasantness using MANCOVA. The only significant difference was for race, and these 2 groups were therefore combined to form a sample of 279 patients with low back pain.

Finally, baseline NPS data were available for 167 patients with osteoarthritis pain from add-on[15] and monotherapy[21] trials (in prior analyses, 162 of these patients who had treatment outcome data available were combined to form a group of patients with osteoarthritis pain[26]).

Statistical Analysis

No attempt had been made in the trials that enrolled patients with low back pain to distinguish neuropathic from non-neuropathic low back pain. However, because patients with neuropathic low back pain probably account for no more than 10%-20% of patients with low back pain,[3,8,29] we first determined whether the sample of patients with low back pain—which may have included some patients with neuropathic low back pain—could be combined with the patients with the inflammatory pain of osteoarthritis. The only significant difference between the patients with osteoarthritis pain and low back pain for the 10 NPS items when t tests were performed was that patients with low back pain rated pain unpleasantness more highly than patients with osteoarthritis pain (Table 1). In addition, to determine whether the patients with osteoarthritis pain and low back pain significantly differed in their profile of responses across the 8 NPS pain quality and spatial items (Fig 1), we performed a MANCOVA with these 8 NPS items as dependent variables, diagnostic group as the independent variable, and age, sex, race, and overall pain intensity and unpleasantness as covariates. The interaction between diagnostic group and NPS items was not significant ($F = .85$; $P = .54$), and the osteoarthritis and low back pain groups were therefore combined to form a sample of patients with non-neuropathic pain that was examined in all subsequent analyses.

To determine whether the patients with neuropathic pain differed from the combined sample of patients with non-neuropathic pain in their responses to the 10 NPS items and in their profile of responses across the 8 NPS pain quality and spatial items, we performed t tests and a MANCOVA with the pain quality and spatial items as dependent variables, diagnostic group as the independent variable, and age, sex, race, and pain intensity and unpleasantness as covariates.

To determine whether pain quality and spatial characteristics contribute to discriminating whether patients have neuropathic vs non-neuropathic pain, we performed a multiple logistic regression analysis in which neuropathic vs non-neuropathic pain was the criterion variable, and the independent effects of the 8 NPS pain quality and spatial items were evaluated after adjusting for age, sex, race, and pain intensity and unpleasantness.

Finally, we determined for each patient which of the 6 NPS pain quality items had been rated highest or tied for highest in intensity. The percentages of patients with neuropathic and non-neuropathic pain who rated each item as their highest were then calculated to determine whether the groups differed with respect to which pain quality items were experienced as the most intense and were compared using chi-squared tests. All statistical analyses were performed using SAS/STAT software version 8.2.[41]

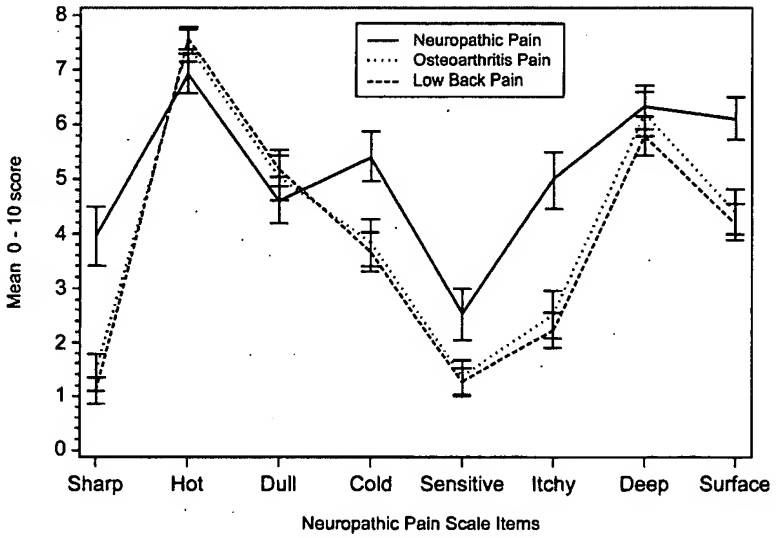

Figure 1. Mean scores for Neuropathic Pain Scale pain quality and spatial items.

Results

Patients with neuropathic pain were older (t [376] = 3.1; $P < .001$), less likely to be women (χ^2 [1] = 7.0; $P < .01$), and more likely to be Caucasian or African-American vs other (χ^2 [1] = 10.4; $P < .01$) than patients with non-neuropathic pain (Table 2). Patients with neuropathic and non-neuropathic pain did not differ significantly in pain intensity and unpleasantness or the pain quality sharp but did differ significantly for the pain qualities hot, dull, cold, sensitive, and itchy, and for both deep and surface pain (Table 3 and Fig 2). Because pain intensity and unpleasantness are critically important in the overall experience of pain[37] and significantly associated with ratings of specific neuropathic pain symptoms,[5] all subsequent analyses were adjusted for both of these NPS items to identify the unique effects of pain quality and spatial characteristics.

In the MANCOVA conducted to compare patients with neuropathic and non-neuropathic pain, the interaction between diagnostic group and NPS items indicated that patients with neuropathic pain differed from those with non-neuropathic pain in their profile of responses across the 8 NPS pain quality and spatial items, adjusting for age, sex, race, and pain intensity and unpleasantness ($F = 36.33$; $P < .0001$).

As can be seen from the results of the multiple logistic regression analysis presented in Table 4, the NPS items hot, dull, cold, sensitive, deep, and surface made independent contributions to whether patients had neuropathic vs non-neuropathic pain, after adjusting for age, sex, race, and pain intensity and unpleasantness. Fig 3

Table 2. Demographic Characteristics of Patients With Neuropathic and Non-neuropathic Pain

	Patients With Neuropathic Pain (N = 172)	*Patients With Non-neuropathic Pain (N = 446)*
Mean age (yrs [SD])**	6.1 (12.2)	56.5 (14.8)
Female (n [%])*	90 (52.3%)	285 (63.9%)
Race/ethnicity (n [%])*		
Caucasian	149 (86.6%)	375 (84.1%)
African-American	21 (12.2%)	38 (8.5%)
Latino, Asian, or other	2 (1.2%)	33 (7.4)%

*$P < .01$, for 2-tailed t tests of differences between patients with neuropathic and non-neuropathic pain.

**$P < .001$, for 2-tailed t tests of differences between patients with neuropathic and non-neuropathic pain.

Table 3. Group Differences in Neuropathic Pain Scale Item Scores in Patients With Neuropathic and Non-neuropathic Pain

	Patients With Neuropathic Pain (N = 172)		*Patients With Non-neuropathic Pain (N = 446)*	
	Mean	*SD*	*Mean*	*SD*
Intense	7.13	1.75	6.91	1.80
Unpleasant	7.45	1.89	7.13	1.88
Sharp	6.33	2.74	5.94	2.91
Hot***	5.41	3.06	3.73	2.93
Dull*	4.61	2.82	5.13	2.73
Cold***	3.94	3.58	1.22	2.17
Sensitive***	4.97	3.48	2.34	2.82
Itchy***	2.51	3.09	1.29	2.18
Deep**	6.94	2.38	7.53	1.83
Surface***	6.11	2.57	4.28	2.76

*$P < .05$, for 2-tailed t tests of differences between patients with neuropathic and non-neuropathic pain.

**$P < .01$, for 2-tailed t tests of differences between patients with neuropathic and non-neuropathic pain.

***$P < .001$, for 2-tailed t tests of differences between patients with neuropathic and non-neuropathic pain.

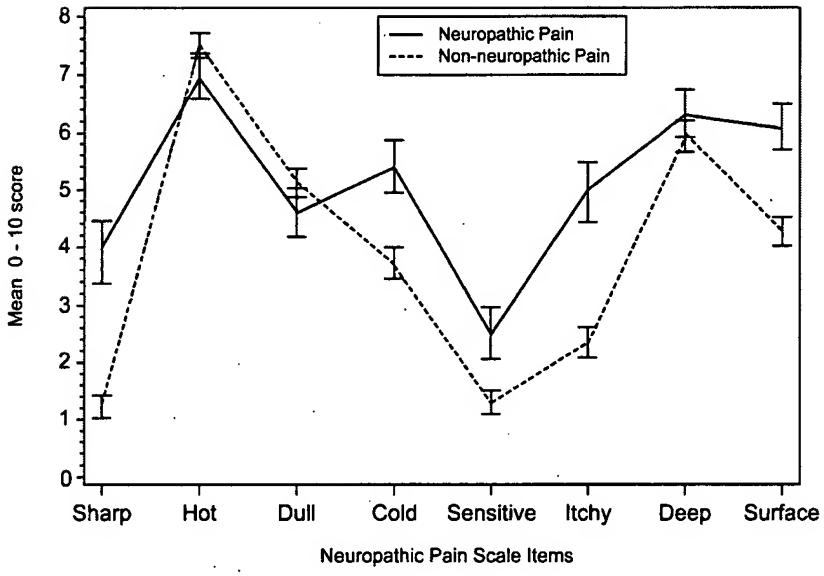

Figure 2. Mean scores for Neuropathic Pain Scale pain quality and spatial items for patients with neuropathic and non-neuropathic pain.

shows that the initial model with the demographic covariates and pain intensity and unpleasantness has balanced sensitivity and specificity of approximately .6, whereas Fig 4 shows that when the pain quality and spatial items are added, the discrimination of the model improves considerably, with balanced sensitivity and specificity of approximately .8. The c statistics presented in Figs 3 and 4 show that the model that includes pain quality and spatial characteristics provides superior discrimination between patients with neuropathic and non-neuropathic pain (c = .5 indicates no ability to discriminate and c = 1.0 indicates perfect discrimination), and the area under the receiver operating characteristic curves of the 2 models differs significantly ($\chi^2 = 70.2$; $P < .0001$).[16]

Table 5 presents the percentages of patients with neuropathic pain and non-neuropathic pain who rated each of the NPS pain quality items as highest (or tied for highest) in intensity. Patients with either neuropathic or non-neuropathic pain were most likely to rate sharp pain as their most intense pain. After sharp pain, however, hot and sensitive pain were the pain qualities rated most intense by patients with neuropathic pain, whereas dull pain was the pain quality rated most intense by patients with non-neuropathic pain.

Discussion

The results of this study demonstrated that specific pain symptoms differ between patients with peripheral neuropathic pain and those with non-neuropathic inflammatory and musculoskeletal pain. Specifically, patients with neuropathic pain reported significantly more intense hot, cold, sensitive, itchy, and surface pain and significantly less intense dull and deep pain than patients with non-neuropathic pain in univariate analyses, and the overall profile of pain quality and spatial character-

Table 4. Logistic Regression Models for Neuropathic vs Non-neuropathic Pain

Variable	B	SE	P	Odds Ratio*
Initial model				
Age	.02	.01	.004	1.02
Sex	−.30	.10	.002	.55
Race (Caucasian vs African-American)	.47	.27	.085	6.61
Race (Latino/Other vs African-American)	−1.42	.50	.004	.09
Pain intensity	.01	.06	.853	1.01
Pain unpleasantness	.11	.06	.071	1.12
Measures of pain quality and spatial characteristics added to the model				
Age	.03	.01	.003	1.03
Sex	−.21	.12	.076	.66
Race (Caucasian vs African-American)	.74	.33	.023	1.13
Race (Latino/other vs African-American)	−1.36	.58	.020	.14
Pain intensity	.03	.10	.792	1.03
Pain unpleasantness	.13	.09	.126	1.14
Sharp	−.05	.05	.324	.95
Hot	.12	.04	.008	1.13
Dull	−.22	.05	<.0001	.81
Cold	.32	.05	<.0001	1.38
Sensitive	.18	.04	<.0001	1.19
Itchy	−.01	.05	.857	.99
Deep	−.35	.08	<.0001	.71
Surface	.13	.05	.017	1.14

*Odds ratios are adjusted for other terms included in the model, and odds ratios for continuous variables reflect the multiplicative increase in odds for neuropathic pain vs non-neuropathic pain for every 1-point change in the variable.

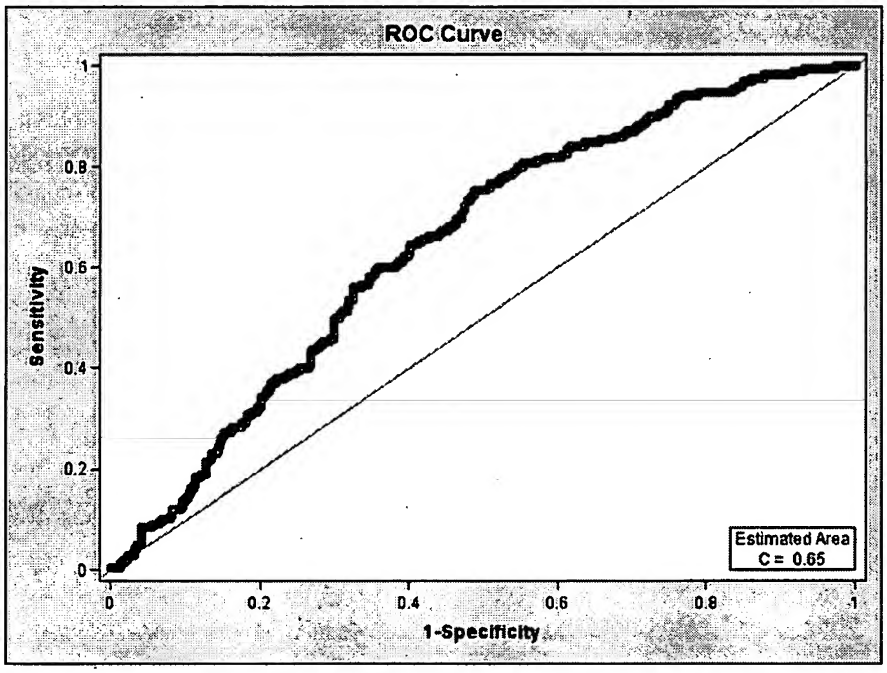

Figure 3. Receiver operating characteristic plot for neuropathic vs non-neuropathic pain logistic regression model with pain intensity and unpleasantness included in the model.

istics differed significantly between these 2 groups of patients controlling for pain intensity and unpleasantness. Moreover, the addition of these specific symptoms (except for itchy) improved the discrimination of patients with neuropathic pain from those with non-neuropathic pain in a logistic regression analysis that adjusted for demographic covariates as well as overall pain intensity and unpleasantness.

Before considering the implications of these results, important limitations of this study must be acknowledged. First, the NPS does not include some symptoms experienced by patients with neuropathic pain (eg, par-

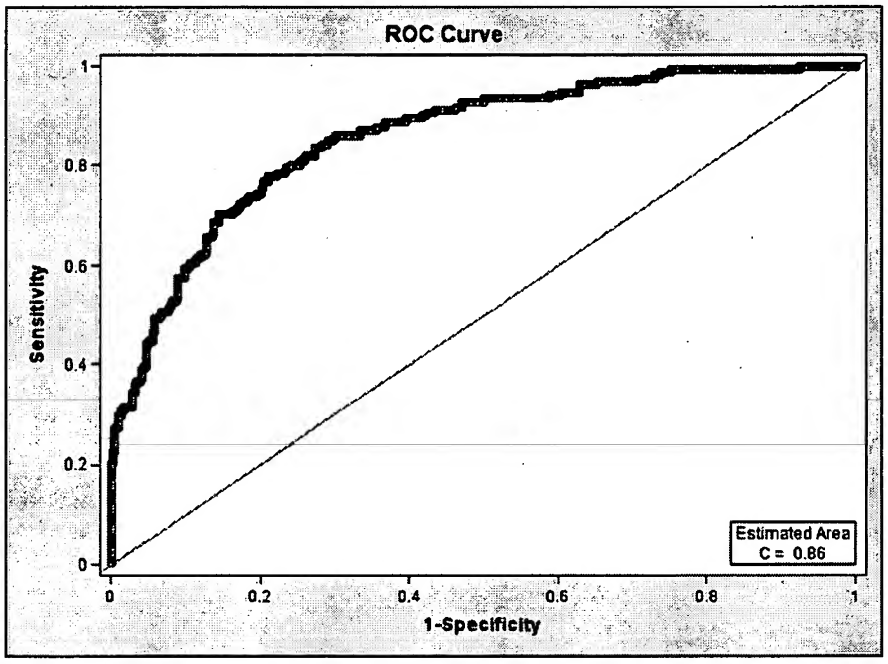

Figure 4. Receiver operating characteristic plot for neuropathic vs non-neuropathic pain logistic regression model with pain quality and spatial characteristics added to the model with pain intensity and unpleasantness.

Table 5. Percentages of Patients Who Rated Each Pain Quality Highest in Intensity*

	Patients With Neuropathic Pain (N = 172)	Patients With Non-neuropathic Pain (N = 446)	Chi-Square
Sharp	45.9	58.1	7.38*
Hot	32.6	15.7	21.75**
Dull	15.7	40.8	34.97**
Cold	23.8	2.0	79.47**
Sensitive	32.6	9.6	48.46**
Itchy	8.1	2.2	11.57**

NOTE. Ties for highest rating were counted twice in calculating percentages; patients were not included in these analyses if they had baseline scores of 0 on all 6 of these items.

*$P < .01$, for 2-tailed t tests of differences between patients with neuropathic and non-neuropathic pain.

**$P < .001$, for 2-tailed t tests of differences between patients with neuropathic and non-neuropathic pain.

esthesias such as numbness and tingling). Moreover, because this measure was initially developed to characterize the symptoms of neuropathic pain, other symptoms common in patients with non-neuropathic pain are not included. Symptoms not captured by the NPS might be important in further characterizing the differences between patients with neuropathic and non-neuropathic pain, and future research should use measures that more comprehensively assess the pain qualities experienced by both types of patients. In addition, because the NPS is a questionnaire, it does not assess allodynia (ie, pain in response to a normally innocuous stimulus) and hyperalgesia (ie, increased pain in response to a painful stimulus), 2 types of stimulus-evoked pain widely considered to be very important signs of neuropathic pain conditions.[7] Any attempt to identify pain mechanisms will need to carefully assess stimulus-evoked pain signs in combination with pain symptoms. It is important to note, however, that patient reports of stimulus-evoked pain are associated with physical examination findings,[13] which suggests that the NPS items "sensitive" and "surface" may reflect, at least in part, stimulus-evoked pain. Finally, the data we examined were drawn from patients enrolled in a series of clinical trials of lidocaine patch 5%. Our results therefore might not be representative of patients in clinical practice or of individuals with the pain conditions we examined who are not seeking medical care and should not be generalized to those groups without further study.

Several important strengths of our study should be emphasized. The sample we examined was large, and all patients were carefully assessed and diagnosed with peripheral neuropathic pain, osteoarthritis, and low back pain to ensure their eligibility for enrollment in phase II and IV clinical trials of these conditions. In addition, it can be assumed that these patients were motivated to complete the NPS in a careful and thoughtful manner, because they had volunteered to participate in a clinical trial. Finally, because of the inclusion criteria used in the clinical trials, all patients had pain that was clinically meaningful in intensity.[1,35,42]

There are several important implications of our results. None of the specific aspects of pain quality and spatial characteristics we examined were pathognomonic for neuropathic vs non-neuropathic pain and all were reported by at least some patients with each of these types of pain as their most intense pain. Interestingly, sharp pain, which has been considered characteristic of neuropathic pain, was most likely to be rated by both groups of patients as their most intense pain and was also the sole symptom that provided no discrimination between the groups in either the univariate or the multivariate analyses. Our results demonstrated, however, that several aspects of pain quality and spatial characteristics do differ significantly between patients with neuropathic and non-neuropathic pain. For example, we found that patients with neuropathic pain were twice as likely as those with non-neuropathic pain to rate hot pain as their most intense pain, which is consistent with the recent observation that the presence of burning pain should alert clinicians to the possibility of a neuropathic pain condition.[31] Furthermore, patients with neuropathic pain were less than half as likely as those with non-neuropathic pain to rate dull pain as their most intense pain, although the average intensity of dull pain in each of these types of patients did not differ greatly.

These data suggest that methods must be developed for characterizing the relative predominance or "profile" of different symptoms and signs to adequately characterize a patient's pain, assist in its diagnosis, and provide guides to underlying mechanisms and treatment targets. We have assumed, however, that the diagnoses of the patients studied reflect distinct mechanisms of neuropathic vs non-neuropathic pain. It has been argued that this assumption can be challenged, particularly with respect to peripheral neuropathic pain and chronic inflammatory pain, because lesions in somatosensory pathways can cause inflammation and inflammatory processes can cause neural damage.[9] Any such overlap of neuropathic and inflammatory mechanisms in patients with peripheral neuropathic pain and those with inflammatory conditions such as osteoarthritis would limit the ability of the NPS and similar measures to distinguish between patients and to identify their underlying mechanisms.

Our objective was to contribute to providing an empirical basis for identifying neuropathic pain mechanisms by characterizing specific pain symptoms reported by patients with neuropathic pain and comparing these to symptoms reported by patients with non-neuropathic inflammatory and musculoskeletal pain. Our results suggest that it might be possible to use self-report measures such as the NPS[20] and similar measures[11-13,30] in the first stage of epidemiologic studies to identify patients with an increased risk of having a neuropathic pain condition. Before beginning such studies, it will be necessary to establish the sensitivity and specificity of these measures when used in community-based samples of individuals with chronic pain. To make a

definitive diagnosis of neuropathic pain, however, a second assessment stage would be required that included a physical examination and other measures necessary for a differential diagnosis.[38]

A mechanism-based approach to the treatment of neuropathic and non-neuropathic pain will require: 1) knowledge of the pathophysiologic mechanisms of human clinical pain conditions; 2) medications with known analgesic mechanisms of action that target these pain mechanisms; and 3) reliable and valid methods for identifying these mechanisms in individual patients. Although progress has been made in accomplishing the first of these goals,[46,49] the results of recent research suggest that targeting drug action to neuropathic pain mechanisms will be challenging without increased knowledge of both pain and drug mechanisms.[25,39,43] It has been even more difficult, however, to identify the mechanisms that account for an individual patient's pain.[28,34,48] Just as the diagnosis of neuropathic pain cannot be made by evaluating only symptoms, identification of the mechanisms of pain will require additional procedures, including assessment of stimulus-evoked pain, sensory testing, pharmacologic challenges, and punch skin biopsy. Our results indicate that a comprehensive assessment of pain symptoms, which adjusts for overall pain intensity and unpleasantness, is likely to be an important component of the identification of pain mechanisms.

References

1. Anderson KO: Role of cutpoints: Why grade pain intensity? Pain 113:5-6, 2005

2. Argoff CE, Galer BS, Jensen MP, Oleka N, Gammaitoni AR: Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: Assessment with the Neuropathic Pain Scale. Curr Med Res Opin 20(Suppl 2):S21-S28, 2004

3. Atkinson JH, Slater MA, Williams RA, Zisook S, Patterson TL, Grant I, Wahlgren DR, Abramson I, Garfin SR: A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. Pain 76:287-296, 1998

4. Backonja MM, Krause SJ: Neuropathic Pain Questionnaire–Short Form. Clin J Pain 19:315-316, 2003

5. Backonja MM, Stacey B: Neuropathic pain symptoms relative to overall pain rating. J Pain 5:491-497, 2004

6. Barbano RL, Herrmann DN, Hart-Gouleau S, Pennella-Vaughan J, Lodewick PA, Dworkin RH: Effectiveness, tolerability, and impact on quality of life of lidocaine patch 5% in diabetic polyneuropathy. Arch Neurol 61:914-918, 2004

7. Baumgärtner U, Magerl W, Klein T, Hopf HC, Treede RD: Neurogenic hyperalgesia versus painful hypoalgesia: Two distinct mechanisms of neuropathic pain. Pain 96:141-151, 2002

8. Bennett GJ: Neuropathic pain: An overview, in Borsook D (ed): Molecular Neurobiology of Pain. Seattle, WA, IASP Press, 1997, pp 109-113

9. Bennett GJ: Can we distinguish between inflammatory and neuropathic pain? Pain Res Manage, 11(Suppl A):11A-15A, 2006

10. Bennett M: The LANSS Pain Scale: The Leeds assessment of neuropathic symptoms and signs. Pain 92:147-157, 2001

11. Bennett MI, Smith BH, Torrance N, Potter J: The S-LANSS score for identifying pain of predominantly neuropathic origin: Validation for use in clinical and postal research. J Pain 6:149-158, 2005

12. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, Cunin G, Fermanian J, Ginies P, Grun-Overdyking A, Jafari-Schluep H, Lanteri-Minet M, Laurent B, Mick G, Serrie A, Valade D, Vicaut E: Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain 114:29-36, 2005

13. Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 108:248-257, 2004

14. Boureau F, Doubrere JF, Luu M: Study of verbal description in neuropathic pain. Pain 42:145-152, 1990

15. Burch F, Codding C, Pate N, Sheldon E: Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients. Osteoarthritis Cartilage 12:253-255, 2004

16. DeLong ER, DeLong DM, Clarke-Pearson DL: Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 44:837-845, 1988

17. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, Bushnell MC, Farrar JT, Galer BS, Haythornthwaite JA, Hewitt DJ, Loeser JD, Max MB, Saltarelli M, Schmader KE, Stein C, Thompson D, Turk DC, Wallace MS, Watkins LR, Weinstein SM: Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. Arch Neurol 60:1524-1534, 2003

18. Galer BS, Gammaitoni AR, Mollen M, Seiden D, White W, Drass M, Dworkin RH, Simpson D, Domingos J, Ma T: Lidocaine patch 5% versus gabapentin versus the combination in diverse peripheral neuropathic pain: Results of a double-blind, double-dummy, randomized, placebo-controlled trial. Presented at the 6th International Conference on the Mechanisms and Treatment of Neuropathic Pain, San Francisco, CA, September 18-20, 2003

19. Galer BS, Gammaitoni AR, Oleka N, Jensen MP, Argoff CE: Use of the lidocaine patch 5% in reducing intensity of various pain qualities reported by patients with low-back pain. Curr Med Res Opin 20(Suppl 2):S5-S12, 2004

20. Galer BS, Jensen MP: Development and preliminary validation of a pain measure specific to neuropathic pain: The Neuropathic Pain Scale. Neurology 48:332-338, 1997

21. Galer BS, Sheldon E, Pate N, Codding C, Burch F, Gammaitoni AR: Topical lidocaine patch 5% may target a novel underlying pain mechanism in osteoarthritis. Curr Med Res Opin 20:1455-1458, 2004

22. Gammaitoni AR, Galer BS, Onawola R, Jensen MP, Argoff CE: Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: Results of a pilot 2-week, open label study using the Neuropathic Pain Scale. Curr Med Res Opin 20(Suppl 2):S13-S19, 2004

23. Gimbel J, Linn R, Hale M, Nicholson, B: Lidocaine patch treatment in patients with low-back pain: Results of an open-label, nonrandomized, pilot study. Am J Ther 12:311-319, 2005

24. Herrmann DN, Barbano RL, Hart-Gouleau S, Pennella-Vaughan J, Dworkin RH: An open-label study of the lidocaine patch 5% in painful idiopathic sensory polyneuropathy. Pain Med 6:379-384, 2005

25. Herrmann DN, Pannoni V, Barbano RL, Pennella-Vaughan J, Dworkin RH: Skin biopsy and quantitative sensory testing do not predict response to the lidocaine patch in painful neuropathies. Muscle Nerve, 33:42-48, 2006

26. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, Galer BS: Assessment of pain quality in chronic neuropathic and nociceptive pain clinical trials using the Neuropathic Pain Scale. J Pain 6:98-106, 2005

27. Jensen MP, Dworkin RH, Gammaitoni AR, Olaleye DO, Oleka N, Galer BS: Do pain qualities and spatial characteristics make independent contributions to interference with physical and emotional functioning? J Pain, 7:644-653, 2006.

28. Jensen TS, Baron R: Translation of symptoms and signs into mechanisms in neuropathic pain. Pain 102:1-8, 2003

29. Katz J, Pennella-Vaughan J, Hetzel RD, Kanazi GE, Dworkin RH: A randomized, placebo-controlled trial of bupropion SR in chronic low back pain. J Pain 6:656-661, 2005

30. Krause SJ, Backonja M: Development of a Neuropathic Pain Questionnaire. Clin J Pain 19:306-314, 2003

31. Marchettini P: The burning case of neuropathic pain wording. Pain 114:313-314, 2005

32. Masson EA, Hunt L, Gem JM, Boulton AJM: A novel approach to the diagnosis and assessment of symptomatic diabetic neuropathy. Pain 38:25-28, 1989

33. Melzack R: The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1:277-299, 1975

34. Otto M, Bak S, Bach FW, Jensen TS, Sindrup SH: Pain phenomena and possible mechanisms in patients with painful polyneuropathy. Pain 101:187-192, 2003

35. Paul SM, Zelman DC, Smith M, Miaskowski C: Categorizing the severity of cancer pain: Further exploration of the establishment of cutpoints. Pain 113:37-44, 2005

36. Petersen KL, Fields HL, Brennum J, Sandroni P, Rowbotham MC: Capsaicin evoked pain and allodynia in post-herpetic neuralgia. Pain 88:125-133, 2000

37. Price DD: Psychological Mechanisms of Pain and Analgesia. Seattle, IASP Press, 1999

38. Rasmussen PV, Sindrup SH, Jensen TS, Bach FW: Symptoms and signs in patients with suspected neuropathic pain. Pain 110:461-469, 2004

39. Rasmussen PV, Sindrup SH, Jensen TS, Bach FW: Therapeutic outcome in neuropathic pain: Relationship to evidence of nervous system lesion. Eur J Neurol 11:545-553, 2004

40. Rowbotham MC, Baron R, Petersen KL, Fields HL: Spectrum of pain mechanisms contributing to PHN, in Watson CPN, Gershon AA (eds): Herpes Zoster and Postherpetic Neuralgia, 2nd ed. New York, NY, Elsevier, 2001, pp 39-64

41. SAS Institute: SAS/STAT User's Guide, Version 8. Cary, NC, SAS Institute, 1999

42. Serlin RC, Mendoza TR, Nakamua Y, Edwards KR, Cleeland CS: When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. Pain 61: 277-284, 1995

43. Wasner G, Kleinert A, Binder A, Schattschneider J, Baron R: Postherpetic neuralgia: topical lidocaine is effective in nociceptor-deprived skin. J Neurol 252:677-686, 2005

44. White WT, Patel N, Drass M, Nalamachu S: Lidocaine patch 5% with systemic analgesics such as gabapentin: A rational polypharmacy approach for the treatment of chronic pain. Pain Med 4:321-330, 2003

45. Wilkie DJ, Huang HY, Reilly N, Cain KC: Nociceptive and neuropathic pain in patients with lung cancer. J Pain Sympt Manage 22:899-910, 2001

46. Woolf CJ: Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med 140:441-451, 2004

47. Woolf CJ, Bennett GJ, Doherty M, Dubner R, Kidd B, Koltzenburg M, Lipton R, Loeser JD, Payne R, Torebjork E: Towards a mechanism-based classification of pain? Pain 77: 227-229, 1998

48. Woolf CJ, Mannion RJ: Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 353: 1959-1964, 1999

49. Woolf CJ, Max MB: Mechanism-based pain diagnosis. Anesthesiology 95:241-249, 2001